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Risk factors associated with the deterioration of renal function after kidney transplantation

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Risk factors associated with the deterioration of renal function after kidney transplantation. Renal function early after transplantation is associated with a large number of risk factors, including donor age and acute rejection. During the 1990s, donor age increased and the incidence of acute rejection decreased. Renal function between the third and sixth month improved slightly, while renal function deterioration between the third or sixth month and the 12th month improved significantly. This modification coincides with the introduction of mycophenolate mofetil and tacrolimus. The tendency for sustained renal improvement early after transplantation became more evident after the introduction of anti-calcineurin–free regimens. Studies of protocol biopsies have shown that there is an increase of glomerular volume after transplantation and that a larger glomerular volume at 4 months is associated with a better glomerular filtration rate. This adaptation mechanism is impaired in patients with chronic allograft nephropathy or in patients with high cyclosporin levels. Taken together, these data suggest that the steady improvement of renal allograft function may be partly explained by a better glomerular adaptation after transplantation because of the avoidance of the vasoconstrictive effect of anti-calcineurinic agents, and a significant decrease in the prevalence of chronic allograft nephropathy early after transplantation.

Epidemiologic studies have shown that renal allograft survival is associated with a large number of risk factors, such as donor or recipient age, sex, and race, or comorbid conditions, type of donor (living vs. cadaver), cause of donor death (stroke vs. trauma), panel reactivity antibodies, and the presence of delayed graft function or acute rejection. However, one of the most powerful predictors of graft outcome is renal allograft function. Moreover, renal function is also a major determinant of patient survival [1, 2]. Thus, it has been suggested that strategies to improve renal function after transplantation may contribute to increased patient and allograft survival.

Key words: renal transplantation, renal function.

PREDICTIVE VALUE OF RENAL FUNCTION ON PATIENT AND GRAFT SURVIVAL

The gold standard to measure renal function is the glomerular filtration rate (GFR), evaluated according to the inulin clearance or an isotopic method. Because these procedures cannot be applied in the clinical setting because of their cost and complexity, different formulas have been developed to estimate GFR that take into account clinical and analytical parameters. However, the agreement between predicted and measured GFR is rather low. It has been recently shown that the proportion of predicted GFR differing from inulin clearance by ± 10 mL/min/1.73 m^2 ranged from 34% to 53% depending on the formula applied [3]. These results suggest that estimated GFR cannot substitute the determination of real GFR, at least in clinical trials. A second consequence of these observations is that the predictive value of renal allograft function on graft or patient outcome has probably been underestimated in epidemiologic studies.

One strategy to improve the predictive value of renal function on graft and patient outcome is to separate the evolution of renal function into two parameters: serum creatinine (SCr) or estimated GFR at 3 or 6 months, which roughly represents the early adaptation of the renal allograft after transplantation, and the evolution of renal function between this early period and the 12th month, the so-called δSCr or δGFR, which represents the risk for further renal allograft deterioration [1, 4]. This strategy is based on the observation that there is a very weak correlation between SCr or estimated GFR early after transplantation and δSCr or δGFR. For example, Gourishankar et al [5] did not find any association between 6-month GFR and the slope of GFR after the sixth month in a study including 429 cadaver renal recipients transplanted at a single center. In a multicenter study performed in Spain that included 3365 patients who received a single kidney in 1990, 1994, and 1998 that was functioning at the end of the first year [2], the correlation between SCr at 3 months and δSCr was weak despite being significant ($r^2 = 0.099$). Similarly, when GFR was estimated by means of the Cockroft-Gault formula, the

correlation between GFR at 3 months and δGFR did not improve ($r^2 = 0.108$). Thus, it is not surprising that both the SCr and δSCr or GFR and dGFR parameters are independent predictors of patient and allograft survival [1, 2].

FACTORS ASSOCIATED WITH SCR AND δSCR

Renal function during the first year is associated with different risk factors. In the Spanish Study of Chronic Allograft Nephropathy, the following covariates were associated with an increased SCr at 3 months: older donor age, female donor sex, stroke as a cause of donor death, male recipient sex, cold ischemia time, the presence of delayed graft function, acute rejection, cytomegalovirus infection, and re-intervention for any reason. However, only two factors were associated with δSCr deterioration between the third and 12th month: acute rejection and recipient hepatitis C virus antibodies [4]. These data show that acute rejection is not only associated with an irreversible decline of renal function early after transplantation, but also with an accelerated renal allograft function deterioration, probably reflecting that acute rejection triggers immune mechanisms that continue to harm the kidney, far beyond the apparent resolution of the acute rejection episode. These data also indicate the importance of hepatitis C virus infection that contributes to renal function deterioration because of sustained renal allograft immune-mediated damage. It is important to note that these two covariates were also major independent predictors of death-censored allograft survival.

In a study that included 85,135 patients from the Organ Procurement and Transplantation Network/United Network for Organ Sharing with a functioning graft at the end of the first year, risk factors associated with SCr >1.5 mg/dL were evaluated and compared with risk factors associated with renal allograft survival. The following covariates were associated with elevated serum creatinine at 1 year, graft survival, and death-censored graft survival: older donor age, black donor race, younger recipient age, black recipient race, male recipient sex, delayed graft function, and the presence of acute rejection. Because risk factors for 1-year renal allograft dysfunction and graft failure were similar, the possible utility of 1-year SCr as a surrogate marker of renal allograft outcome was suggested [6]. However, when power calculations were performed to calculate minimum sample size in a hypothetical trial in which 1-year serum creatinine could be considered the primary efficacy variable, the sample size was rather large, raising doubts about the utility of serum creatinine at 1 year as a useful end point [7].

EVOLUTION OF RENAL FUNCTION AFTER TRANSPLANTATION SINCE 1990

There is some discrepancy in the studies describing how renal function has evolved in recent years in transplanted patients. In the United States, 1-year SCr steadily improved between 1988 and 1998 from 1.82 ± 0.82 mg/dL to 1.67 ± 0.82 mg/dL [1]. In a study describing the evolution of 6-month GFR between 1991 and 2000, the improvement of 6-month GFR occurred during a discrete period of time, ranging between 1994 and 1997. Before and after this period, GFR remained stable, and this improvement coincided with the introduction of mycophenolate mofetil and tacrolimus [8]. Gourishankar et al have observed that, although 6-month creatinine clearance remained stable between 1990 and 2000, the slope of the creatinine clearance after the sixth month improved. The kidneys that were transplanted before 1997 significantly deteriorated over time. For the period from 1990 to 1993, the mean creatinine clearance slope was −0.34 mL/min/month, and for the period from 1994 to 1997, it was −0.20 mL/min/month. In contrast, mean GFR slope improved by +0.29 mL/min/month during the period from 1998 to 2000.

In Spain, SCr at 3 months has been slightly modified during the last decade. The lowest SCr was observed in 1990 (1.59 ± 0.64 μmol/L), the highest in 1994 (1.72 ± 0.73 μmol/L), and an intermediate value was observed in 1998 (1.65 ± 0.66 μmol/L). However, while δGFR between the third and 12th month deteriorated −0.8 mL/min/1.73 m^2 in 1990 and −0.4 mL/min/1.73 m^2 in 1994, it improved 1.0 mL/min/1.73 m^2 in 1998. Again, in 1990 and 1994, the use of mycophenolate mofetil and tacrolimus was negligible in Spain. However, despite raising optimistic expectations [1], these tendencies for better renal function preservation have not been associated with any important modification of long-term renal allograft survival [9]. During the 1990s, important modifications in donor and recipient characteristics occurred. While acute rejection was reduced, donor quality worsened and recipient age increased. These modifications may offset the beneficial effects of new treatments for graft outcome [1, 2, 8].

IMMUNOSUPPRESSIVE TREATMENT AND RENAL FUNCTION

Since the introduction of mycophenolate mofetil and tacrolimus, δGFR has significantly improved [4, 5, 8, 10]. It has been suggested that this improvement is related to the superior immunosuppressive activity of these drugs that allow a reduction in the incidence of not only acute rejection [11, 12], but also subclinical rejection [13, 14]. Furthermore, it has been suggested that both treatments may decrease the rate of progression of chronic allograft nephropathy (CAN) [13, 15, 16]. This tendency for a better preservation of renal function became more evident after the introduction of sirolimus. In a prospective, randomized study evaluating cyclosporin (CsA) withdrawal at 3 months from sirolimus treatment, CsA, and a steroid-based regimen, it was observed that

renal function steadily improved in patients in the CsA withdrawal group, while renal function deteriorated in patients on CsA and sirolimus. At 36 months, estimated GFR was 47 mL/min/1.73 m^2 in patients on CsA and 59 mL/min/1.73 m^2 in patients without CsA [17]. Similarly, in a prospective randomized trial comparing an anti-calcineurin inhibitor (anti-CNI)–free regimen based on sirolimus, mycophenolate mofetil, and prednisone with an anti-CNI–based regimen consisting of CsA, mycophenolate mofetil (MMF), and prednisone, renal function steadily increased during the first 36 months in the anti-CNI–free group, while it steadily deteriorated in patients in the CNI-based regimen [18]. These data indicate the contribution of anti-CNI toxicity in progressive renal allograft function deterioration.

CORRELATION BETWEEN RENAL FUNCTION AND HISTOLOGIC LESIONS

In stable renal allografts, it has been observed that the correlation between structure and function is much weaker than expected. For example, in a study in which a protocol biopsy was done at 3 months, serum creatinine was 125 ± 35 μmol/L in patients without CAN and 145 ± 35 μmol/L in patients with CAN ($P = 0.008$). Despite this difference, it was observed that the predictive value of CAN on graft survival was independent of either graft function or proteinuria, suggesting that histology evaluated early after transplantation contains relevant information to predict graft survival that is different from the information contained in surrogate variables of renal function [19]. This observation was confirmed in a larger study [20].

The notion that there is a poor correlation between structure and function in stable grafts is further reinforced by a study that included 32 CsA-treated patients with serum creatinine <200 μmol/L and proteinuria <1 g/24 hours, in whom a protocol biopsy was done at 5 months. In these patients, renal function was measured with inulin clearance. Additionally, effective renal plasma flow, renal functional reserve after amino acid infusion and after simultaneous amino acid, and dopamine infusion were determined. When patients were classified according to the presence or absence of CAN, no differences were observed between both groups [21]. Furthermore, in a study of serial protocol biopsies performed at 4 and 14 months, chronic lesions significantly progressed in the different renal compartments, while SCr remained stable [22]. Taken together, these data suggest that renal function does not properly reflect structural damage early after transplantation, at least when biopsies are evaluated according to Banff criteria, and raise the question of whether more precise evaluation of renal structural damage may allow a better understanding of the relationship between structure and function in stable grafts.

RELATIONSHIP BETWEEN GLOMERULAR NUMBER, GLOMERULAR VOLUME, AND RENAL FUNCTION IN STABLE GRAFTS

Studies performed on autopsy specimens have shown that glomerular number in patients without a history of renal disease shows a great variability, ranging approximately between 200,000 and 1,800,000 [23, 24]. In these studies, an inverse relationship between glomerular number and glomerular volume has been described, suggesting that glomerular enlargement represents an adaptation mechanism to provide normal patients with a sufficient filtration surface area and, accordingly, it may be considered a rough surrogate measure of glomerular number [24]. Aging is associated with decreased glomerular number and increased glomerular volume; moreover, susceptibility to renal disease is associated with low glomerular endowment [25–27]. Similarly, in renal transplants, larger glomerular size evaluated in donor biopsies is associated with late renal allograft dysfunction [28]. In epidemiologic studies, surrogate measures of transplanted renal mass are associated with decreased allograft survival [29], and in an experimental setting, transplanted renal mass is a major determinant of graft survival [30]. These data suggest that estimation of glomerular number in renal allografts may be useful to better characterize the relationship between structure and function in patients with transplants.

Because the gold standard method of counting glomeruli can only be applied in autopsy studies, glomerular number can be estimated in vivo only if the following parameters are known: mean glomerular volume, cortical glomerular volume fraction, and the absolute volume of renal cortex [31]. The first two parameters can be estimated in a renal biopsy applying a morphometric technique, and the second can be obtained with magnetic resonance imaging. This approach has been applied to estimate glomerular number in stable grafts at 4 months to better characterize anatomo-clinical correlations. A total of 39 patients with a serum creatinine <200 μmol/L and proteinuria <1 g/24 hours were included. A few days after the protocol biopsy, inulin clearance was determined and renal magnetic resonance imaging was performed. The mean glomerular number was $0.73 \pm 0.33 \times 10^6$ (range, 0.21-1.66). Mean GFR was 56 ± 15 mL/min/1.73 m^2 (range, 39-79). There was an association between glomerular number and GFR ($r = 0.47$, $P = 0.002$), showing that the number of transplanted glomeruli is a major determinant of renal function after transplantation.

GLOMERULAR ADAPTATION AFTER RENAL TRANSPLANTATION

Glomerular adaptation to body growth during childhood or adaptation after renal ablation is characterized by glomerular enlargement. Renal transplants receive

only half the glomerular number. After transplantation, the kidney is exposed to different insults such as ischemia-reperfusion injury, acute rejection, and drug nephrotoxicity, which may reduce the capacity of glomeruli to adapt to the recipient metabolic demand. To evaluate glomerular adaptation after transplantation, Vg (glomerular volume) has been measured in paired donor and 4-month protocol biopsies [32]. It was observed that glomeruli enlarge during this early period from $4.1 \pm 1.4 \times 10^6$ μm^3 to $5.1 \pm 2.4 \times 10^6$ μm^3. Furthermore, a positive association between glomerular size at 4 months and estimated GFR according to the Cockroft-Gault formula ($r = 0.38$, $P = 0.01$) was described, suggesting that glomerular adaptation is a necessary condition to achieve a better renal function early after transplantation. Interestingly, glomerular enlargement was observed in patients without chronic lesions in the protocol biopsy, but not in patients displaying CAN.

The long-term consequences of this adaptation process have not been characterized. Despite graft function as a determinant of graft survival, there is a size threshold for glomerular enlargement that leads to glomerulosclerosis and progressive renal failure, which has to be taken into consideration [33]. To evaluate the relative contribution of renal function and glomerular volume on graft survival in stable grafts, we evaluated 144 patients in whom an early protocol biopsy with sufficient tissue was available. Patients were divided into four groups according to glomerular volume and renal function. The outcome was excellent in patients with small glomeruli ($<5 \times 10^6$ μm^3) and good renal function (estimated GFR >60 mL/min/1.73 m^2) and was the poorest in patients with large glomeruli and poor renal function. Graft survival was intermediate in the other two groups (unpublished observation). We interpreted this to mean that recipients with small glomerular volume and good renal function may represent patients endowed with a large number of glomeruli and, accordingly, the filtration surface area was sufficient to provide an adequate renal function. In contrast, recipients with large glomeruli and poor renal function may represent those patients who, despite adaptation, had insufficient filtration surface area to provide an adequate renal function. However, we were intrigued with the group of patients with small glomeruli and poor renal function. This situation suggested that their capacity to adapt after transplantation was impeded. When the four groups were compared, CsA exposure was higher in patients with poor renal function and small glomeruli. These data suggest that CsA prevents glomerular adaptation to recipient metabolic demand.

CONCLUSION

Glomerular enlargement is associated with better renal function after transplantation. This adaptation mechanism does not occur in patients already displaying CAN or in patients with high CsA exposure. In the last decade, a steady increase of δGFR after the third month has been observed. This modification was first described after the introduction of mycophenolate mofetil and tacrolimus, which prevent nephrotoxicity and decrease the incidence of CAN. However, after the introduction of calcineurin-free regimens based on sirolimus, this effect has become more evident. Thus, we may speculate that the steady increase of renal function observed in the last decade may be partly explained by a better glomerular adaptation after transplantation due to the avoidance of the vasoconstrictive effect of anti-calcineurinic agents and a significant decrease in the prevalence of CAN early after transplantation.

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